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Alveolar Soft Part Sarcoma in Children and Adolescents: Clinical Features and Outcome of 11 Patients

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The clinical features and response to therapy of pediatric alveolar soft part sarcoma, a rare soft tissue sarcoma of uncertain histogenesis, have not been previously described in detail in the literature. We retrospectively reviewed the clinical characteristics of all patients with alveolar soft part sarcoma who were seen at our institution over a 32-year period. We found 11 patients with the diagnosis of alveolar soft part sarcoma. Their ages ranged from 2.8–16 years (median 9.8). Staging was determined using the Intergroup Rhabdomyosarcoma Study clinical grouping system and the UICC TNM system. Accordingly, there were six patients with grossly resected tumors (clinical groups I and II) and five with unresected or metastatic disease (clinical groups III and IV). Children with resected disease were more likely to have smaller noninvasive tumors. The main feature predictive of survival was tumor resectability, since chemotherapy in various combinations failed to produce significant tumor responses. Nine patients are disease-free with a median follow-up of 11.9 years. Surgical resection remains the mainstay of therapy for pediatric alveolar soft part sarcoma. Since active chemotherapy agents have not been identified, patients with unresected or metastatic disease may benefit from experimental agents. The survival rate of this cohort is superior to that seen in adults.

Key words: alveolar soft part sarcoma in children

INTRODUCTION

Alveolar soft part sarcoma, a rare soft tissue neoplasm of uncertain histogenesis, accounts for 5% of pediatric nonrhabdomyosarcoma soft tissue sarcomas [1]. Histologically, the tumor is characterized by polygonal cells arranged in a glomerular or pseudoalveolar pattern with marked vascular invasion [2–4]. PAS staining reveals intracellular glycogen and diastase-resistant crystalline material. Immunohistochemical analysis is inconclusive, since both neural and muscle markers have been observed. Neuron specific enolase, S-100, and desmin have been positive in 25–40% of cases. MyoD has been recently identified in these tumors as well, and actin has been found to be a component of the intracytoplasmic crystals [3–5].

Alveolar soft part sarcoma commonly occurs in the second and third decades of life and usually involves the musculoskeletal fascial planes of lower extremities, thighs, and buttocks [2,6]. Chemotherapy has been ineffective in controlling the disease; thus complete surgical resection offers the only hope of prolonged survival. One-third of patients develop lung and brain metastases 10 or more years following diagnosis, necessitating an extended period of follow-up [6,7].

Several series have examined the clinical presentation and survival of patients with alveolar soft part sarcoma, yet the natural history, response to therapy, and prognosis of this tumor in the pediatric population have not been specifically addressed. We report the clinical characteristics, treatment, and outcome of 11 children and adolescents with alveolar soft part sarcoma who were treated at our institution over a 32-year period.

MATERIALS AND METHODS

Patients

A review of the records of all children with solid tumors who were treated at St. Jude Children's Research

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TABLE I. Characteristics, Treatment, and Outcome of Pediatric Alveolar Soft Part Sarcoma*

Patient	Age at diagnosis (Yr	Mo)	Sex	Race	Primary site	IRS stage	TNM stage	Treatment (response)	Outcome (years)
1	2	9	F	W	Extremity	I	T1aN0M0	Surgery (CR) VAC (NE) Radiotherapy (NE)	(AD) 11.9
2	14	1	F	W	Trunk	I	T1aN0M0	Surgery (CR)	NED +17.3
3	15	2	M	W	Trunk	I	T1aN0M0	Surgery (CR)	NED +13.6
4	5	10	M	B	Trunk	I	T1bN0M0	Surgery (CR)	NED +14.1
5	4		F	W	Head and neck	I	T1aN0M0	Surgery (CR) Brachytherapy (NE) VIAdr (NE)	NED +0.6
6	10	0	M	W	Trunk	IIb	T1aN1M0	Surgery (CR) VAdrAC (NE)	NED +18.6
7	9	7	M	W	Head and neck	III	T1bN1M0	VAdrAC (SD) Surgery (CR)	NED +20.4
8	8	5	F	W	Head and neck	III	T1aN0M0	ICarE (SD) Surgery (PR) Radiotherapy (CR)	NED +2.4
9	15	4	F	W	Extremity	III	T1bN0M0	VIAdr (SD) Surgery (CR) Radiotherapy (NE)	NED +2
10	5	2	F	W	Extremity	IV	T1bN0M1	Surgery (local CR) VIAdr (SD lung) Thoracotomy (CR) Radiotherapy (NE)	NED +1
11	16	0	M	W	Extremity	IV	T2bN0M1	VAdrAC (PD) ICarE (SD) Top (PD) Radiotherapy (PR primary)	DOD 1.1

*CR = complete response; NE = not evaluable; SD = stable disease; PR = partial response; PD = progressive disease; AD = accidental death; NED = no evidence of disease; DOD = died of disease; V = vincristine; A = actinomycin D; C = cyclophosphamide; Adr = doxorubicin; I = ifosfamide; Car = carboplatin; Top = topotecan.

Hospital from 1962 through December 1994 identified 11 patients with the diagnosis of alveolar soft part sarcoma. The diagnosis was confirmed in all cases by one of the authors (D.M.P.) using previously defined histopathologic criteria [2].

Disease stage was determined at the time of initial evaluation of surgery using the Intergroup Rhabdomyosarcoma Study clinical grouping criteria [8]. Briefly, patients with clinical group I disease had completely resected tumors; group II patients had grossly resected tumors with microscopic residual disease at the primary site (IIa), or regional nodal involvement that was either completely resected (IIb) or grossly removed with evidence of microscopic residual tumor (IIc); patients with group III disease had gross residual tumor; and patients with metastatic disease were designated as group IV.

Tumor size, nodal involvement, and degree of tumor invasiveness were categorized according to the Tumor-Node-Metastases system of the UICC [9] by review of operative notes, radiologic material, and gross pathologic tumor material (when available). T1 lesions were defined as those confined to the organ of origin; T2 lesions invaded contiguous organs. Both categories were further classified by maximum tumor diameter as a (<5 cm) or b (> 5 cm). Nodal involvement was designated N1 (nonnodal involvement = N0) and distant metastases at the time of diagnosis as M1 (vs. M0).

Treatment

Children with clinical group I and II disease (n = 6) were treated with primary surgical resection of the tumor. In one of these children (patient 6; see Table I), en bloc resection of the primary tumor revealed an adherent tumor-infiltrated lymph node. A subsequent radical neck dissection failed to disclose any other nodal disease. Two patients (1 and 5) received adjuvant radiotherapy because of inadequate surgical margins. In addition, patients 1, 5, and 6 received adjuvant combination chemotherapy (Table I).

There were three children with clinical group III disease. Two (patients 7 and 9) received preoperative doxorubicin-containing regimens in an attempt to assess chemotherapy responsiveness of the primary tumor and to determine whether these children would benefit from postoperative chemotherapy (Table I). Two patients received radiotherapy because of residual tumor after che-

motherapy and surgery (patient 8) or close surgical margins (patient 9). Patient 7 had a palpable neck node at diagnosis, which was removed and found to be replaced with tumor. Subsequent radical neck lymph node dissection failed to disclose any other involved nodes.

Children with metastatic disease at diagnosis (n = 2) were treated with combined modality therapy, which included radiation therapy, chemotherapy, and surgery.

RESULTS

Patient characteristics, therapy, and outcome of the 11 cases are shown in Table I. Median age at diagnosis was 9.6 years (range 2.8–16). Sex and race distribution included six females and one black patient. Tumors originated in the extremities (n = 4), trunk (n = 4), and head and neck area (n = 3). Six patients had localized disease (clinical groups I and II), three had gross residual tumor, and two had distant metastases. Regional lymph nodes were involved at diagnosis in two (patients 6 and 7). Ten children had T1 lesions. Tumors measured <5 cm in five of six children with clinical group I and II disease, but in only one of five patients with advanced disease (clinical groups III and IV).

Nine of 11 patients survive disease free with a median follow-up of 11.9 years (range 0.6–20.4). The main feature predictive of survival was tumor resectability. All children in whom complete surgical resection was feasible are alive (patients 2–10), except one who was disease-free at the time of death (patient 1). Chemotherapy in various combinations (including vincristine, dactinomycin, doxorubicin, cyclophosphamide, ifosfamide, etoposide, carboplatin, and topotecan) failed to produce significant clinical response in the five patients with gross residual or metastatic disease.

DISCUSSION

We have described the clinical features of pediatric alveolar soft part sarcoma, with a median 12-year follow-up. The most common primary tumor sites were the trunk and extremity, as reported in a mixed study of adult and pediatric patients [6]. In three cases, the tumor originated in the head and neck area, a site commonly reported in young patients [2,6]. In contrast with other series, no sex predominance was observed. Only two of our 11 patients had metastatic disease at diagnosis, a figure similar to the 5 of 25 patients <20 years old reported by Lieberman [6].

Nine of 11 patients survive disease-free with a median follow-up of 11.9 years following diagnosis. The estimated 12-year survival rate is 74% ± 15% (see Fig. 1). These findings are consistent with other series in which younger age at diagnosis conferred a favorable prognosis. This difference in outcome may be attributable to a higher prevalence of small noninvasive lesions or differences in

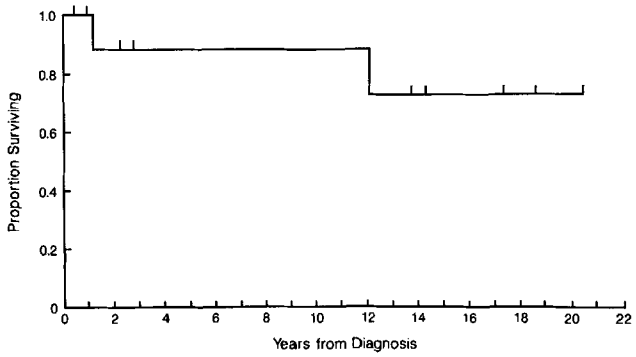

Fig. 1. Kaplan-Meier survival estimate of 11 children with alveolar soft part sarcoma.

the biology of pediatric alveolar soft part sarcoma. We recognize, however, that four of our patients have been followed for a relatively short period of time and that late recurrences characterize this tumor.

In the Pediatric Oncology Group (POG) classification scheme of pediatric nonrhabdomyosarcoma soft tissue sarcomas, alveolar soft part sarcoma is classified as a high grade (grade 3) neoplasm [10]. Its designation as a high grade lesion stems from Lieberman's series in which adults with alveolar soft part sarcoma had a dismal prognosis [6]. However, Enzinger and Weiss [2] have emphasized that this neoplasm has a good prognosis in children, an observation supported by our present series. If these results are confirmed in studies that include larger numbers of children, it would be reasonable to propose a revised histologic grading system for pediatric alveolar soft part sarcoma.

Surgery remains the therapy of choice for patients with alveolar soft part sarcoma. The tumor should be excised with a 2 cm margin of normal surrounding tissue whenever feasible and lymph node sampling may be performed if the primary tumor is within the contiguous area of the lymph node drainage [1]. None of our patients with unresected or disseminated disease responded to combination chemotherapy, even when regimens included agents known to be active against adult soft tissue sarcomas, such as ifosfamide and doxorubicin [11]. We could not assess the value of adjuvant chemotherapy in prolonging survival in our patients with completely resected tumors; however, several adult trials have failed to show a significant survival advantage. In a recently reported Pediatric Oncology Group study, patients with completely resected grade 3 lesions fared significantly worse than those with grade 1 or 2 lesions, suggesting that a subset of patients may benefit from adjuvant chemotherapy [12]. Given the disappointing responses to chemotherapy in our group of patients with this disease and the excellent outcome of patients with completely resected tumors, we cannot recommend the routine use of cur-

rently available adjuvant chemotherapy. Since no effective drug combinations are available at present, we propose that newly diagnosed patients with unresectable or metastatic alveolar soft part sarcoma be enrolled in Phase I and II chemotherapy trials in an attempt to identify novel active agents. This approach has proven successful in children with rhabdomyosarcoma [13].

Local failures have been reported to occur in up to 20% of patients with alveolar soft part sarcoma [6]. Recently, Sherman et al. [14] documented excellent local control in six adult patients with this neoplasm who received adjuvant or preoperative radiotherapy and thus recommended that all adult patients with localized disease receive radiation therapy. We cannot recommend the routine use of radiotherapy in children with completely resected tumors in which the margin of resection is adequate; local control was not a problem in our patients, and the long-term side effects of radiotherapy in the growing child (limb length discrepancies, second malignant neoplasms) may outweigh its benefits. We do recommend radiotherapy for patients with inadequate surgical margins, microscopic residual tumor, and as palliative therapy in patients with metastatic disease in selected sites. More recently, preoperative radiotherapy has shown promising results in adults with a variety of soft tissue sarcomas, and this approach deserves further testing in children who present with nonmetastatic unresectable alveolar soft part sarcoma [15].

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NOTE ADDED IN PROOF

Subsequent to the submission of this manuscript, patient no. 9 developed pulmonary metastases.

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